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(56) Documents Cited
GB 2075503 A
J. Endocrinology 158(3), R1-R5 (Sept 1998)

(58) Field of Search
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(54) Abstract Title
EP4 Receptor antagonists as bone resorption inhibitors

(57) EP4 receptor antagonists are used in the preparation of a medicament for the treatment of conditions with accelerated bone resorption such as osteoarthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia. Particularly useful agents are the prostaglandin derivatives disclosed in GB 2075503 such as [1α(Z),2β,5α)-(±)- and [1R[1α(Z),2β,5α]]-(-) -7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-2-(morpholinyl)-3-oxocyclopentyl]-4-heptenoic acids.

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MEDICAL USE

The present invention relates to the use of EP4 receptor antagonists in the treatment of conditions with accelerated bone resorption.

The EP4 receptor is a 7TM and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP1, EP2 and EP3). Although PGE_2 is known to be a stimulator of osteoclastogenesis and it is known to stimulate bone resorption in vivo, the significance of the EP receptor sub-types in this disease is not known. It is also not known whether antagonists at any of the EP receptors would inhibit bone resorption.

It has now been found that the EP4 receptor plays a critical role in osteoclast-like cell formation from bone marrow by PGE_2 and therefore antagonists at the EP4 receptor are useful in the treatment of conditions with accelerated bone resorption.

The invention accordingly provides, in a first aspect, the novel use of EP4 antagonists in the treatment of conditions with accelerated bone resorption.

There is also provided as a further aspect of the invention the use of EP4 antagonists in the preparation of a medicament for use in the treatment of conditions with accelerated bone resorption.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, suffering from or susceptible to conditions with accelerated bone resorption, comprising administration of an effective amount of an EP4 antagonist.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.

EP4 antagonists have been shown to have utilty in conditions with accelerated bone resorption as indicated by for example their ability to inhibit PGE_2 - stimulated osteoclast-like cell formation in mouse bone marrow.

The treatment of conditions with accelerated bone resorption mentioned hereinbefore includes the treatment of osteo arthritis, rheumatoid arthritis, osteoporosis, inflammatory bone diseases and hypocalcemia.

Suitable EP4 antagonists for use in the present invention include [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof and [1R[1α(Z),2β,5α]]-(-)-7-[5-[[1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof which are selective antagonists at the EP4 receptor.

[1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof and [1R[1α(Z),2β,5α]]-(-)-7-[5-[[1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof may be prepared and formulated according to the methods described in UK Patent Application No GB 2075503.

For example EP4 antagonists may be formulated for oral, buccal, parenteral, depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose). Oral and parenteral formulations are preferred.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with

pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The EP4 antagonists may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The EP4 antagonists may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The EP4 antagonists may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the EP4 antagonists may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

Suitable dose ranges are described in the art, that is to say that for use in conditions with accelerated bone resorption the compounds may be used at doses appropriate for other conditions for which EP4 antagonists are known to be useful. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient, and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected. A suitable dose range is for example 0.1 mg/kg to about 200 mg/kg, e.g. 0.1 mg/kg to 10 mg/kg, bodyweight per day.

The EP4 antagonists useful in the instant invention may, if desired, be administered in combination with one or more other therapeutic agents and formulated for administration by any convenient route in a conventional manner. Appropriate doses will be readily appreciated by those skilled in the art.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. The claims may take the form of product, composition, process or use claims and may include, by way of example, one or more of the following claims.

Claims

1. The use of an EP4 antagonist in the preparation of a medicament for use in the treatment of conditions with accelerated bone resorption.

2. A method for the treatment of a mammal. including man, suffering from or susceptible to conditions with accelerated bone resorption, comprising administration of an effective amount of an EP4 antagonist.

3. The use or method according to claim 1 or 2 wherein the EP4 antagonist is [1α(Z),2β,5α]-(±)-7-[5-[[(1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof and [1R[1α(Z),2β,5α]]-(-)-7-[5-[[1,1'-Biphenyl)-4-yl]methoxy]-2-(4-morpholinyl)-3-oxocyclopentyl]-4-heptenoic acid and the physiologically acceptable salts and solvates thereof.

The Patent Office

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Claims searched: 1-3

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Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

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Int Cl (Ed.6): A61K 31/557

Other: WPI, DIALINDEX (MEDICINE), CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	GB 2075503 A (GLAXO) see page 2 lines 32-40	
A	J. Endocrinology 158(3), R1-R5 (Sept 1998) (K. ONO et al) "Important role of EP4, a subtype of prostaglandin (PG) E receptor"	

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.